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# Gamma-aminobutyric acid as a bioactive compound in foods: a review

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ABSTRACT

Gamma-aminobutyric acid (GABA) is a non-protein amino acid, considered a potent bioactive compound. GABA has been widely studied because of its numerous physiological functions and positive effects on many metabolic disorders. One the most important of these is the hypotensive effect that has been demonstrated in animals and in human intervention trials. The biosynthesis of GABA and its optimization, without affecting sensory characteristics, are the key in obtaining GABA-enriched food products that have health benefits. Lactic acid bacteria (LAB) are the main GABA-producers and therefore there are a wide range of GABA-enriched fermented food products, in which GABA is natural, safe and eco-friendly. Increasing knowledge of bioactive components in food has opened avenues for the development of new, naturally occurring functional food with added value for health.


## 1. Introduction

Although GABA has been widely studied in medical and pharmaceutical fields, this article focuses on enhanced GABA levels in food products, its biosynthesis and physiological function, mainly when it is consumed, its optimization, and future beneficial effects in the food industry.

GABA is a four-carbon free amino acid that is widely present in bacteria, plants and vertebrates. In plants and bacteria it plays a metabolic role in the Krebs cycle, and in vertebrates it acts as a potent neural signal transmitter. GABA is primarily formed by the irreversible α-decarboxylation reaction of L-glutamic acid or its salts, catalysed by glutamic acid decarboxylase enzyme (GAD; EC 4.1.1.15) (Fig. 1) (Satya Narayan & Nair, 1990) whose biochemical properties have been characterized (Nomura, Nakajima, Fujita, & Kobayashi, 1999). This enzyme has been found in bacteria such as LAB (Bertoldi, Carbone, & Borri-Voltattorni, 1999), *Escherichia* (Rice, Johnson, Dunnigan, & Reasoner, 1993), *Streptococcus*, *Aspergillus* (Kato, Furukawa, & Hara, 2002) and *Neurospora* (Kubicek, Hampel, & Rohr, 1979); in plants such as tea (Zhao et al., 2011), tomato (Yoshimura et al., 2010), soybean (Serraj et al., 1998), mulberry leaf (Yang, Jhou, & Tseng, 2012), germinated brown rice (Dai-xin, Lu, Lan, Li-te, & Yong-Qiang, 2008) and petunia (Johnson, Narendra, Joe, Cherry, & Robert, 1997); and in mammalian animal brain (Nathan et al., 1994). GABA is also found in insects such as cockroach, grasshopper, moth, honeybee and fly (Anthony, Harrisson, & Sattelle, 1993). However, studies have mostly focused on GABA-producing microorganisms rather than GABA in isolation. LAB (Maras, Sweeney, Barra, Bossa, & John, 1992) and yeast (Hao & Schmit, 1993) are the most important GABA producers, because they are commercially useful as starters in fermented foods.

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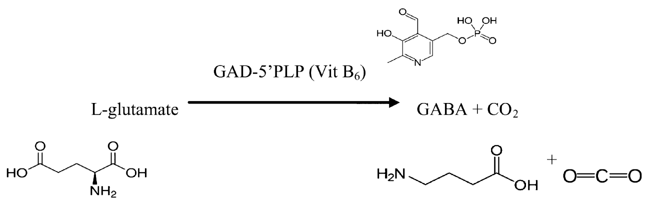


**Fig. 1 – Decarboxylation reaction of L-glutamate to GABA catalysed by glutamate decarboxylase (GAD), which is dependent on the cofactor pyridoxal-5′-phosphate or vitamin $B_6$.**

### 1.1. *Physiological functions*

There is considerable knowledge about the multiple physiological functions of GABA. As a result, the development of functional foods containing GABA has been actively pursued (Saikusa, Horino, & Mori, 1994). In animals, GABA is found at high concentrations in the brain and plays a fundamental role in inhibitory neurotransmission in several of its routes within the central nervous system, and also in peripheral tissues (DeFeudis, 1981). Alterations in GABAergic circuits are associated with Huntington's disease, Parkinson's disease, senile dementia, seizures, Alzheimer's disease, stiff person syndrome and schizophrenia (Wong, Bottiglieri, & Snead, 2003), because the GAD substrate (L-glutamate) acts as an excitant of human neurons and its product (GABA) acts as an inhibitor (Battaglioli, Liu, & Martin, 2003). One alteration can be caused by very low GABA content in the brain, which is observed in patients with Alzheimer's disease (Seidl, Cairns, Singewald, Kaehler, & Lubec, 2001). Okada et al. (2000) demonstrated that a daily oral administration of rice germ containing 26.4 mg GABA was effective in treating these neurological disorders. Indeed, the practice of yoga *asana* sessions increases GABA levels in the brain, and is a potential treatment for some autonomic disorders that are commonly observed in menopausal and presenium periods (Streeter et al., 2007).

Other physiological functions such as relaxation (Wong et al., 2003), sleeplessness and depression (Okada et al., 2000) have been treated with GABA. Very recently, Wu et al. (2014) showed the GABA content in a variety of tea and demonstrated the sleep-promoting effect of GABA. This bioactive compound could potentially protect against chronic kidney disease, ameliorate oxidative stress induced by nephrectomy (Sasaki et al., 2006), and activate liver and kidney function (Sun, 2004). GABA has been shown to naturally enhance immunity under stress conditions within one hour of its administration in humans (Abdou et al., 2006). GABA may also be useful for alcohol-related disease prevention and treatment (Oh, Soh, & Cha, 2003b). Furthermore, this amino acid contributes to increasing the concentration of growth hormone in plasma and the rate of protein synthesis in the brain (Tujioka et al., 2009). Recent studies also indicate that it is a potent secretor of insulin, and thus could help to prevent diabetes (Adeghate & Ponery, 2002). Other authors suggested that GABA tea ameliorates diabetic-induced cerebral autophagy and therefore may possess the potential on the therapy of diabetic encephalopathy (Huang et al., 2014).

GABA could delay or inhibit the invasion and metastasis of various types of cancer cells, such as mammary gland, colon and hepatic cancer cells (Kleinrok, Matuszek, Jesipowicz, Opolski, & Radzikowski, 1998; Minuk, 2000; Opolski, Mazurkiewicz, Wietrzyk, Kleinrok, & Radzikowski, 2000). Furthermore, consumption of GABA-enhanced brown rice can inhibit leukaemia cell proliferation and has a stimulatory action on cancer cell apoptosis (Oh & Oh, 2004). GABA has also been considered a potential tumour suppressor for small, airway-derived lung adenocarcinoma (Schuller, Al-Wadei, & Majidi, 2008). In addition, it has anti-inflammatory and fibroblast cell proliferation activities, which promote the healing of cutaneous wounds (Han, Kim, Lee, Shim, & Hahm, 2007). Besides, this amino acid is involved in maintaining cell volume homeostasis under UV radiation (Warskulat, Reinen, Grether-Beck, Krutmann, & Häussinger, 2004), in the synthesis of hyaluronic acid, and in enhancing the rate of dermal fibroblasts exposed to oxidative stress agents (Ito, Tanaka, Nishibe, Hasegawa, & Ueno, 2007), which makes GABA a potential novel application for dermatological purposes (Di Cagno et al., 2009). Kelly and Saravanan (2008) reported that GABA may reduce inflammation in rheumatoid arthritis and attenuate the metabolic response to ischemic incidents (Abel & McCandless, 1992). It also affects the control of asthma (Xu & Xia, 1999) and breathing (Kazemi & Hoop, 1991).

Several reports have referred to the link between GABA and mood disorders. Low GABA in plasma may be a biological marker of vulnerability to the development of various mood disorders. As Petty (1994) showed, plasma concentrations of GABA were significantly lower than control values in patients with major bipolar disorder and manic-depressive illness. Krystal et al. (2002) demonstrated that normal GABA levels may reflect effective antidepressant treatments and seizure control, and are a target for the treatment of bipolar disorder. Moreover, plasma GABA levels may correlate with aggressiveness in some patients with depression, mania and alcoholism (Bjork et al., 2001). There is a relationship between progesterone, GABA, and mood behaviour in women (Rapkin, 1999). Hormone secretion may also be regulated by GABA, as shown by Parkash and Kaur (2007). Furthermore, there is clinical evidence of the regulation of thyroid hormones and GABA systems. Thyroid dysfunction (i.e. hyperthyroidism or hypothyroidism) acts on the GABA system. It particularly affects enzyme activities that are responsible for the synthesis and degradation of GABA and GABA receptor expression and function. In the developing brain, hypothyroidism generally decreases enzyme activities and GABA levels, whereas in the adult brain, hypothyroidism tends to increase enzyme activities and GABA levels (Wiens & Trudeau, 2006). Furthermore, recently, Xie, Xia and Le (2014) demonstrated that GABA improves oxidative stress and functions of thyroids and thyroid hormones explaining lowered weight gains and suggesting GABA as a preventer of obesity. Other authors demonstrated GABA as a bioactive compound present in brown rice and germinated brown rice may mediate anti-obesity effects through the peroxisome proliferator-activated receptor gamma gene (Imam et al., 2014). Other studies have suggested that GABA could improve visual function in senescent animals (Leventhal, Wang, Pu, Zhou, & Ma, 2003) and even enhance memory (Kayahara & Sugiura, 2001). Finally, there is evidence of GABA acting as a signal between cell-to-cell

**Table 1 – Physiological functions of GABA tested on animals and humans.**

| Physiological function | Specific function | Reference |
|---|---|---|
| Neurotransmission | Inhibitory neurotransmitter | Battaglioli et al., 2003; DeFeudis,1981 |
| Blood pressure regulator | Potent hypotensive agent | Abe et al., 1995; Aoki et al., 2003; Hayakawa et al., 2004; Inoue et al., 2003; Joye et al., 2011; Kajimoto et al., 2004; Matsubara et al., 2002; Noguchi et al., 2007; Pouliot-Mathieu et al., 2013; Sasaki et al., 1996; Shimada et al., 2009; Tsai et al., 2013; Yamakoshi et al., 2007; Yang et al., 2012; Yoshimura et al., 2010; Wang et al., 2010; Watanabe et al., 2003 |
| Brain diseases | Action on neurological disorders | Okada et al., 2000; Seidl et al., 2001; Wong et al., 2003; Streeter et al., 2007 |
| | Enhances memory | Kayahara & Sugiura, 2001 |
| Psychiatric diseases | Action on mood disorders | Bjork et al., 2001; Krystal et al., 2002 |
| | Relaxing effect | Wong et al., 2003 |
| | Action on sleeplessness | Okada et al., 2000 |
| | Antidepression | Krystal et al., 2002; Okada et al., 2000 |
| | Prevention and treatment of alcoholism | Bjork et al., 2001; Oh et al., 2003a |
| Vital organs | Action on chronic kidney disease | Sasaky et al., 2006; Sun, 2004 |
| | Activates liver function | Sun, 2004 |
| | Improves visual function | Leventhal et al., 2003 |
| | Increases rate secretion protein in brain | Tujioka et al., 2009 |
| Immune system | Enhances immunity | Abdou et al., 2006 |
| Protective against cancer | Delays and/or inhibits cancer cells proliferation | Kleinrok et al., 1998; Minuk, 2000; Opolski et al., 2000 |
| | Stimulatory action on cancer cells apoptosis | Oh & Oh, 2004 |
| | Potent tumour suppressor | Schuller et al., 2008 |
| Cell regulator | Keeps cell volume homeostasis | Warskulat et al., 2004 |
| | Anti-inflammation and fibroblast cell proliferation | Han et al., 2007 |
| | Synthesis of hyaluronic acid | Ito et al., 2007 |
| | Enhances the rate of dermal fibroblasts | Ito et al., 2007 |
| | Quorum sensing signal cell-to-cell | Chevrot et al., 2006 |
| Protector of CVD | Reduces inflammation in rheumatoid arthritis | Kelly & Saravanan, 2008 |
| | Attenuates the metabolic response to ischemic incidence | Abel & McCandless, 1992 |
| | Preventer of obesity | Imam et al., 2014 |
| Respiratory diseases | Control in asthma | Xu & Xia, 1999 |
| | Control on breathing | Kazemi & Hoop, 1991 |
| Hormonal regulator | Increases growth hormone | Tujioka et al., 2009 |
| | Regulation of hormone secretion | Parkash & Kaur, 2007 |
| | Regulation of progesterone | Rapkin, 1999 |
| | Regulation of thyroid hormone | Wiens & Trudeau, 2006 |
| | Potent secretor of insulin | Adeghate et al., 2002 |
| | Preventer of obesity | Xie et al., 2014 |

eukaryotes and pathogenic bacteria controlling the level of quorum-sensing signal cells (Chevrot et al., 2006).

All these physiological functions (data are summarized in Table 1) mean that GABA enriched foods are the natural way to obtain food products with any or low cost added in the production. Chemical addition increase significantly the product price. The products can be available if they pass the food normative. There are a vast variety of GABA-enhanced food products, including: cereals, sourdough and breads, cheeses, fermented sausages, teas, vegetables, legumes, dairy and soy products, alcohol beverages and traditional Asian fermented food.

#### 1.1.1. *GABA as a potent hypotensive agent*

Blood pressure regulation is the most important effect of GABA. Numerous studies have shown that GABA can reduce high blood pressure in animals and humans. Table 2 shows some of the tests that have demonstrated the hypotensive effect of GABA.

The blood pressure (BP) in spontaneously hypertensive rats (SHR) and in hypertensive humans decreases in response to the consumption of GABA-rich food, as shown by Hayakawa et al. (2004) and Kajimoto et al. (2004), respectively. Arterial pressure and heart rate were reduced by direct injection of GABA (50–200 μg) in Wistar rats (Sasaki et al., 1996). Systolic blood pressure (SBP) in SHR was notably reduced after 8 weeks of oral administration of GABA and peptide-enriched soymilk drink (Liu et al., 2011). Moreover, a rat fed a GABA-enriched soy sauce diet for 6 weeks also showed a decrease in SBP (Yamakoshi et al., 2007). Another GABA-enriched fermented soybean diet was efficient in the reduction of BP in SHR (Aoki et al., 2003). The effect of GABA-enriched soybean powder on lowering BP in SHR was also reported by Shizuka et al., 2004. Furthermore, Abe et al. (1995) reported that green tea rich in GABA decreased BP in young and old salt-sensitive rats. In addition, mulberry leaf extract containing GABA lowered blood pressure in SHR in a dose-dependent manner (Yang et al., 2012),

**Table 2 – Some tests of GABA as hypotensor agent.**

| Intake matrix | GABA dosage | Type of animal | Reference |
|---|---|---|---|
| Fermented milk | 0.5 mg | Rat | Hayakawa et al., 2004 |
| Direct injection | 50–200 μg | Rat | Sasaki et al., 1996 |
| Soymilk drink | 1.36 mg/kg BW/day | Rat | Liu et al., 2011 |
| Soy sauce | 0.33 ml/kg BW (containing 1% of GABA) | Rat | Yamakoshi et al., 2007 |
| Tempeh-like fermented soybean | nr | Rat | Aoki et al., 2003 |
| Soybean powder | 0.15% | Male rat | Shizuka et al., 2004 |
| Green tea | 4 mg | Rat | Abe et al., 1995 |
| Mulberry leaf aqueous extract | 2–20 mg/kg BW | Male rat | Yang et al., 2012 |
| Potato snack | 1.7 mg/kg BW | Rat | Noguchi et al., 2007 |
| Purple sweet potato fermented milk | 60 μg–600 μg GABA/ml | Rat | Tsai et al., 2013 |
| Fermented milk | nr | Human | Kajimoto et al., 2004 |
| Fermented milk | 100 ml (containing 10–12 mg of GABA) | Human | Inoue et al., 2003 |
| Cheese | 50 g (containing 16 mg of GABA) | Human | Pouliot-Mathieu et al., 2013 |
| Tomato | 2 and 10 g tomato/kg BW (containing 180% of GABA) | Rat | Yoshimura et al., 2010 |
| Algae | 20 mg | Human | Shimada et al., 2009 |
| Mushroom (*Agaricus blazei*) | nr | Human | Watanabe et al., 2003 |
| Dietary supplementation | 80 mg | Human | Matsubara et al., 2002 |
| Breakfast cereals | 30 g (containing 66 ppm) | Human | Joye et al., 2011 |
| Fermented vinegar and dried bonito drinking water | 70 mg GABA | Human | Tanaka et al., 2009 |

SHR, spontaneously hypertensive rats; nr, not reported; BW, body weight.

and a red algae extract (Porphyra) significantly lowered BP in the same kind of rats (Umekawa et al., 2008). A single administration of GABA-enriched potato snack (1.7 mg/kg BW) reduced blood pressure in a dose-dependent way in rats with normal blood pressure (Noguchi, Nakamura, Nagai, Katsuda, & Koga, 2007), and a recent article reported that a dose of purple sweet potato fermented milk had an antihypertensive effect in SHR (Tsai, Chiu, Ho, Lin, & Wu, 2013).

In human intervention trials, daily intake for 12 weeks of 100 ml of fermented milk containing between 10 and 12 mg of GABA reduced BP in hypertensive patients (Inoue et al., 2003). Moreover, 50 g of GABA-enriched cheese (containing 16 mg of GABA) lowered SBP by 5.5 ± 3.9 mmHg in men (Pouliot-Mathieu et al., 2013). In a single administration study, treatment with a GABA-enriched tomato cultivar elicited a significant decrease in SBP compared to the control group (Yoshimura et al., 2010). The antihypertensive effect in humans has also been studied with an algae enriched with GABA, which reduced BP after oral administration (20 mg of GABA) for 12 weeks. Therefore, its use as a dietary supplement has been proposed (Shimada et al., 2009). Moreover, a mushroom species (*Agaricus blazei*) with enhanced levels of GABA had an antihypertensive effect on mild hypertensive human subjects (Watanabe et al., 2003). Dietary supplementation of 80 mg of GABA also reduced BP in adults with mild hypertension (Matsubara et al., 2002). Other authors suggested that the daily consumption of one portion (30 g) of GABA-enriched breakfast cereals lowered BP (ca. 10 mg) (Joye, Lamberts, Brijs, & Delcour, 2011).

### *1.2. Mechanism underlying GABA effects in human health*

GABA, which is synthesized in the brain, works by blocking brain signals (neurotransmissions). Factors such as guidance of pre- and postsynaptic neurons as well as receptor development and localization are necessary for the correct establishment and function of synapses. Approximately 60–75% of all synapses in the central nervous system are GABAergic (Schwart, 1988). GABA has a pronounced effect on these events and elicits differentiation of neurons; that is, GABA acts as a trophic signal. Accordingly, activating pre-existing GABA receptors, a trophic GABA signal enhances the growth rate of neuronal processes, facilitates synapse formation, and promotes synthesis of specific proteins. Transcription and the novo synthesis are initiated by the GABA signal, but the intracellular link between GABA receptor activation and DNA transcription is largely unknown. The GABA receptors, which recognize and bind GABA, are located in the postsynaptic membrane and are categorized into three major groups: A or alpha, B or beta and C or gamma (with subunits that further determine its pharmacological activity). For example, a select number of benzodiazepines have a tendency to strongly bind with the alpha 1 subunit, while others bind to different alpha subunits. GABA-A receptors mediate fast inhibitory synaptic transmissions; they regulate neuronal excitability and rapid changes in mood. Thus, the seizure threshold, anxiety, panic and response to stress are regulated by GABA-A receptors (Borden, Murali Dhar, & Smith, 1994). GABA-B receptors mediate slow inhibitory transmissions, which appear to be important in memory, mood and pain (Meldrum & Chapman, 1999). GABA-C receptors have been identified, but their physiological role has not yet been described. Nevertheless, the blood–brain barrier is impermeable to GABA and its concentration in the brain is not changed following injection (Hayakawa et al., 2004). Thus, other effects seen following administration of GABA are due to its actions within the peripheral tissues (blood vessels or autonomic nervous system). GABA can inhibit the perivascular nerve stimulation-induced increase in perfusion pressure and also accompany-

ing noradrenaline release from sympathetic nerve fibres of the mesenteric arterial bed through an action on presynaptic $GABA_B$ receptors (Hayakawa et al., 2002). Together with its neurological effects, GABA demonstrates effects on the endocrine system. However, most of the clinical applications of GABA are purely theoretical, based on word-of-mouth clinical experience or data extrapolated from drug studies. A large scale clinical study on a plethora of endocrine and psycho-neurological conditions is needed.

## 2. GABA production

In the last decade, natural ways to synthesize GABA have been proposed. Most are based on LAB GABA-producing ability, but other microorganisms such as fungi and other bacterial genera have also been used. In addition, GABA metabolism in plants has been studied, which may be another way to easily obtain the amino acid. Furthermore, marine-derived GABA is found to be a good source of functional food ingredients (Harnedy & Fitzgerald, 2012). Indeed, the optimization and enhancement of GABA production has been reported through various novel techniques. These include immobilized cell technology, coculturing GABA-producing strains, and improving a great variety of medium cultures of cells, since the chemical addition of the amino acid is considered unnatural and unsafe (Kim, Lee, Ji, Lee, & Hwang, 2009; Li & Cao, 2010; Seok et al., 2008).

### 2.1. GABA production by lactic acid bacteria

It is difficult to extract GABA from microorganisms because of the low content in natural biological tissues, and chemical synthesis has been rejected because of the corrosive reactants that are used. However, various studies have reported GABA-producing ability by lactic acid bacteria species/subspecies and the presence of GAD activity in their cells. Vast concentrations of gamma-aminobutyric acid production by LAB have also been shown. *Lactobacillus brevis* PM17, *Lactobacillus plantarum* C48, *Lactobacillus paracasei* PF6, *Lactobacillus delbrueckii* sbsp. *bulgaricus* PR1 and *Lactococcus lactis* PU1 isolated from several types of cheeses produced GABA concentrations from 15 to 63 mg/kg in different culture media (Siragusa et al., 2007). Among *L. brevis* strains, *L. brevis* OPY-1 and *L. brevis* OPK-3 isolated from kimchi produced 0.825 g/l and 2.023 g/l, respectively (Park & Oh, 2005, 2007). *L. brevis* NCL912 from Poacai produced 35.66 g/l (Li, Qiu, Gao, & Cao, 2009b) and *L. brevis* GABA057 produced 23.40 g/l. In addition, *L. brevis* GABA100 produced 27.6 mg/ml in black raspberry juice (Kim et al., 2009) and *L. brevis* BJ20 produced 2.465 mg/L in a fermented sea tangle solution (Lee et al., 2010). *L. brevis* IFO 12005 produced 1.049 g/l (Yokoyama, Hiramatsu, & Hayakawa, 2002) and, recently, Diana et al. (2014) found 100 mg/l of GABA produced by *L. brevis* CECT8183 isolated from an artisan Spanish cheese. *L. brevis* CGMCC1306 isolated from fresh milk produced one of the highest concentrations found (76.36 g/l) (Huang, Mei, Sheng, Yao, & Lin, 2007b; Huang, Mei, Wu, & Lin, 2007a). There are many other publications showing GABA production from different lactic acid species isolated from kimchi (Cho, Chang, & Chang, 2007; Lu, Chen, Gu, & Han, 2008; Seok et al., 2008), koumiss (Sun et al., 2009), cheese starter (Nomura, Kimoto, Someya, & Furukawa, 1998), Myanmar fermented tinfoil barb (Su, Takeshi, & Tianyao, 2011), red seaweed beverage (Ratanaburee, Kantachote, Charernjiratrakul, Penjamras, & Chaiyasut, 2011), wholemeal wheat sourdough (Rizzello, Cassone, Di Cagno, & Gobbetti, 2008), human intestines and dental caries (Barrett, Ross, O'Toole, Fitzgerald, & Stanton, 2012), carrot leaves (Tamura et al., 2010) and Japanese traditional fermented fish (tuna sushi) (Komatsuzaki, Shima, Kawamotoa, Momosed, & Kimurab, 2005), among others.

LAB's high GABA production is related to the activity of the GAD enzyme in the cells. The concentration of glutamic acid in the food matrix should be high enough. Accordingly, GABA-producing LAB can be used to develop fermented health-oriented food.

### 2.2. GABA production by other microorganisms and plants

Although LAB are the most studied GABA-producers, a number of fungi microorganisms have also been found to contain GABA in their cells. Filamentous fungi such as *Aspergillus nidulans*, *Aspergillus niger* and *Neurospora crassa* were found to have a considerable GABA pool (Kubicek et al., 1979; Schmit & Brody, 1975). Other fungi like *Monascus purpureus* showed GABA production in rice and nutrient culture media (Jannoey et al., 2010; Su, Wang, Lin, & Pan, 2003) and two *Rhizopus microsporus* strains produced high levels of GABA in fermented soybeans (Aoki et al., 2003). Strains isolated from the sea have also been reported. One *Candida* strain and three *Pichia* isolated from the Pacific Ocean near Japan showed high GABA synthesis ability (Guo, Aoki, Hagiwara, Masuda, & Watabe, 2009). Another four strains belonging to the *Saccharomyces* genera from the same marine yeast collection barely produced GABA (Masuda, Guo, Uryu, Hagiwara, & Watabe, 2008). A pseudomonas species isolated from the marine environment also produced the compound (Mountfort & Pybus, 1992).

Apart from LAB, *Streptomyces* genera isolated from tea produced GABA in a nutrient broth (Jeng, Chen, & Fang, 2007) and faecal *Escherichia coli* also synthesized GABA, which suggests that the colon is a potential source of the bioactive component (Mardini, Jumaili, Record, & Burke, 1991).

The role of GABA in plants is still vague, although it is known that their response to stress conditions and during fungal infection involves changes in GABA (Solomon & Oliver, 2001). For example, in response to cold shock or mechanical stimulation, GABA levels in soybean leaves rise 20- to 40-fold within 5 min, up to 1–2 μmol/g FW (Wallace, Secor, & Schrader, 1984). GABA is also involved in plant development and/or differentiation processes (Gallego, Whotton, Picton, Grierson, & Gray, 1995) and reproduction (Yang, 2003). It is well-known that GABA accumulation in plants is important in pH regulation, as GAD is activated by increases in cytosolic levels of $H^+$ or $Ca^{2+}$. GABA storage is also useful in a plant's defence against phytophagous insects and as an alternative way to use glutamic acid. Cultivar and culture conditions have been proposed for GABA accumulation in germinated fava beans (Li et al., 2009a) and in the germination of brown rice (Banchuen, Thammarutwasik, Ooraikul, Wuttijumnong, & Sirivongpaisal, 2010; Oh, 2003).

### 2.3. Mechanisms and techniques to improve GABA production

The key factors that affect GABA production by microorganisms in culture media are pH and the amount of precursor (glutamic acid or its salts) and other culture media additives, such as carbon or nitrogen sources. Other cultivation parameters can be optimized by the biochemical properties of GAD. The optimum pH for glutamate decarboxylase activity is strictly species-dependent. For instance, the optimum pH for *E. coli* is 3.8, while for *N. crassa* and *L. brevis* it is 5.0 and 4.2, respectively (Yang et al., 2006). As the pH in fermentation media changes with time, pH could be adjusted to maintain the most efficient production (Li, Qiu, Huang, & Cao, 2010). Several authors have reported that glutamate addition increases GABA yield in different culture media (Hayakawa, Ueno, Kawamura, Taniguchi, & Oda, 1997; Huang et al., 2007a, 2007b; Komatsuzaki et al., 2005; Li, Bai, Jin, Wen, & Gu, 2010), although the response differs among the strains (Yang et al., 2008). Similarly, pyridoxal 5′ phosphate (PLP) used as a coenzyme to enhance GAD activity increased GABA production during fermentation in some strains (Coda, Rizzello, & Gobbetti, 2010; Komatsuzaki et al., 2005; Yang et al., 2008), but had no effect on grape must fermentation, primarily due to some strains' own production of PLP (Di Cagno et al., 2009).

During the last decade, genetically engineered techniques have been developed to enhance GABA synthesis. A *Bacillus* strain was used to improve GABA in a traditional Korean fermented soybean product by expressing glutamate decarboxylase from a *L. brevis* strain (Park & Oh, 2006). Similarly, the glutamate decarboxylase gene was isolated from a *L. plantarum* to recombine with *Lactobacillus casei* isolated from kimchi (Kook et al., 2010). Recently, *Corynebacterium glutamicum* ATCC 13032 has been genetically engineered to synthesize GABA using endogenous glutamate from a *L. brevis* strain (Shi & Li, 2011).

Another novel and efficient system for raising the GABA level in media is the co-culture of GABA-producing strains. As Watanabe, Hayakawa, and Ueno (2011) reported, two strains separately produced less than 5 mM of GABA. When the strains were cultivated together the GABA content increased to 15 mM. Immobilized cell technology has been reported to be very useful in optimizing GABA production. The technique consists of entrapping high GABA-producing strains on Ca-alginate gel beads (Huang et al., 2007a, 2007b). An efficient technological method at a large scale has been proposed by Zhang, Liu, Yang, Xia, and Rao (2006). It consists of a bioconversion broth for the industrial production of GABA using L-glutamate and the strain *L. plantarum* GB01-21.

## 3. GABA enriched-food: potential applications

Natural GABA was first found as a constituent of tuber tissue in potato (Steward, Thompson, & Dent, 1949). GABA is naturally present in small quantities in many plant sources: in vegetables such as spinach, potatoes, cabbage, asparagus, broccoli and tomatoes; in fruits, such as apples and grapes; and in cereals, for example barley and/or maize (Oh et al., 2003b). Recently, Pradeep, Manisha, and Malleshi (2011) suggested that germinated millets and legumes are a good source of GABA, and supported the development of functional cereal-based foods especially for children and elderly people. A high amount of GABA is found mainly in fermented products, especially fermented dairy products (Hayakawa et al., 2004), soy sauces (Yamakoshi et al., 2007), and cheeses (Siragusa et al., 2007). Generally, the human body can produce its own supply of GABA. However, GABA production is sometimes inhibited by a lack of oestrogen, zinc or vitamins, or by an excess of salicylic acid and food additives (Aoshima & Tenpaku, 1997). Indeed, GABA-enriched food is required because the GABA content in the typical daily human diet is relatively low (Oh, Moon, & Oh, 2003a).

Table 3 shows the GABA-enriched food products described in the literature.

### 3.1. Cereal-based products

Many GABA-enriched food products are cereal-related. Numerous studies have reported the potential use of selected LAB on fermented sourdough, resulting in a GABA-enriched sourdough that could increase the GABA content in the final bread making. Rizzello et al. (2008) reported the highest synthesis of GABA (258.7 mg/kg) in wholemeal wheat sourdough made using selected LAB, compared with other white wheat flours or rye flours. A wide variety of cereals, pseudo-cereals and leguminous flours with well-characterized GABA-producing strains have been used to make GABA-enriched sourdough and bread (504 mg/kg), with a blend of the most suitable cereal flours to be enriched by GABA (chickpea, amaranth, quinoa and buckwheat) (Coda et al., 2010). The highest GABA content ever found was in Bathura sourdough bread (226.22 mg/100 g) (Bhanwar, Bamnia, Ghosh, & Ganguli, 2013), followed by GABA-enriched bread (115 ppm) made with exogenous supplementation of recombinantly produced GAD from *Yersinia intermedia* (Lamberts, Joye, Beliën, & Delcour, 2012). Another study showed the GABA-enrichment of breakfast cereal flakes by recipe and process optimization with the inclusion of bran, quinoa or malt flour, which resulted in a GABA level of 66 ppm, 90 ppm and 258 ppm, respectively (Joye et al., 2011). Oat fermented with a fungi strain (*Aspergillus oryzae*) produced the highest amount of GABA (435.2 μg/g) (Cai et al., 2012). Moreover, by manipulating germination conditions, GABA concentrations have been optimized in different types of cereals. Nagaoka (2005) obtained a wheat germ rich in GABA (163 mg/100 g) and 9.2 mM was reached in barley bran under optimal conditions (Jin, Kim, & Kim, 2013). Maximal optimized GABA production (42.9 mg/100 g) was found in foxtail millet (Bai, Fan, Gu, Cao, & Gu, 2008) and 14.3 mg/100 g was obtained in germinated waxy hull-less barley under controlled conditions (Chung, Jang, Cho, & Lim, 2009). During the last decade, rice has been a focus for GABA-enrichment, in particular germinated brown rice (GBR) that was found to have 10 times more GABA than milled white rice, and 2 times more than brown rice (Patil & Khan, 2011), and even more in controlled parameters such as soaking in water (Saikusa et al., 1994). GABA-enriched brown rice was achieved by proteolytic hydrolysis (2.26 g/100 g) and by high pressure treatment (Kinefuchi, Sekiya, Yamazaki, & Yamamoto, 1999; Zhang, Yao, & Chen, 2006). GABA-enhanced fermented

**Table 3 – GABA-enriched food.**

| Food product | GABA content (mg/kg) | Reference |
|---|---|---|
| Cereal-based | | |
| Wholemeal wheat sourdough | 258.7 | Rizzello et al., 2008 |
| Whole wheat and soya sourdough | 1000 | Diana et al., 2014 |
| *Bathura* sourdough bread | 22.62 | Coda et al., 2010 |
| Bread with *Yersinia* GAD supplementation | 115 | Lamberts et al., 2012 |
| Cereal bran flakes | 66 | Joye et al., 2011 |
| Cereal quinoa flakes | 90 | Joye et al., 2011 |
| Cereal malt flour flakes | 258 | Joye et al., 2011 |
| Fermented oat by *Aspergillus* sp. | 435.2 | Cai et al., 2012 |
| Wheat germ | 1630 | Nagaoka, 2005 |
| Barley bran | 948 | Jin et al., 2013 |
| Foxtail millet | 429 | Bai et al., 2008 |
| Germinated waxy hull-less barley | 143 | Chung et al., 2009 |
| Brown rice by proteolytic hydrolysis | 22.6 | Zhang et al., 2006 |
| Brown rice by high pressure treatment | 130 | Kinefuchi et al., 1999 |
| Glutinous brown rice (Laozao) | nr | Dai-xin et al., 2008 |
| Diary products | | |
| Cheese with *L. lactis* spp. *lactis* as starter | 320 | Pouliot-Mathieu et al., 2013 |
| Cheddar cheese with probiotic strain | 6773.5 | Wang et al., 2010 |
| Yogurt | nr | Park & Oh, 2006 |
| Fermented soya milk | 424.67 | Park & Oh, 2006 |
| Fermented milk from Tibet | nr | Sun et al., 2009 |
| Fermented milk | 970 | Liu et al., 2011 |
| Fermented milk | 102 | Hayakawa et al., 2004 |
| Fermented milk | 100–120 | Inoue et al., 2003 |
| Fermented goat's milk | 28 | Minervini et al., 2009 |
| Fermented milk by strains isolated on old-style cheese | 5000 | Lacroix et al., 2013 |
| Skimmed milk by strains isolated from Italian cheeses | 15–99.9 | Siragusa et al., 2007 |
| Fermented skim milk by *L. helveticus* | 113.35 | Sun et al., 2009 |
| Fermented milk | 120 | Inoue et al., 2003 |
| Fermented milk by *L. plantarum* | 77.4 | Nejati et al., 2013 |
| Fermented milk by LAB combination | 144.5 | Nejati et al., 2013 |
| Fermented skim milk by *L. plantarum* | 970 | Liu et al., 2011 |
| Low fat fermented milk by LAB combination and protease | 806 | Hayakawa et al., 2004 |
| Black soybean milk | 5420 | Ko et al., 2013 |
| Meat, vegetables and legumes | | |
| Meat | 100 | Dai et al., 2012 |
| Fermented pork sausage | nr | Ratanaburee et al., 2013 |
| Fermented pork sausages | 0.124 | Li et al., 2009a |
| Japanese lactic-acid fermented fish | 1300 | Kuda et al., 2009 |
| Red mustard leaf | 1780 | Kim et al., 2013 |
| Cruciferous plants | 300 | Hattori et al., 2005 |
| Vegetables | nr | Okita et al., 2009 |
| *Brassica* product | nr | Norimura et al., 2009 |
| *Adzuki* beans | 2012 | Liao et al., 2013 |
| Soybean nodules | 0.31 | Serraj et al., 1998 |
| Tempeh-like fermented soybean | 3700 | Aoki et al., 2003 |
| Beverages | | |
| White tea | 505 | Zhao et al., 2011 |
| Black raspberry juice | 27,600 | Kim et al., 2009 |
| Fermented grape must | 9 | Di Cagno et al., 2009 |
| Sugar cane juice-milk | 3200 | Hirose et al., 2008 |
| Fermented-pepper leaves based | 263,000 | Song et al., 2014 |
| Fruit juice | 579 | Tamura et al., 2010 |
| Honey-based beverages | nr | Hiwatashi et al., 2010 |
| Beverage (not specified) | 200 | Kanehira et al., 2011 |
| Rice *shochu* distillery lee | 1560.5 | Yokoyama et al., 2002 |
| Other foods | | |
| Potato snacks | 1700 | Nakamura et al., 2006 |
| Chocolate | 2800 | Nakamura et al., 2009 |
| Potatoes | 160–610 | Nakamura et al., 2006 |

nr, not reported.

glutinous brown rice (Laozao) was developed by fermentation with a *Rhizopus* strain at 28.5 °C for 48 h (Dai-xin et al., 2008). GABA has been analysed in several cereals such as brown rice germ, brown rice sprouts, barley sprouts, bean sprouts, beans, corn, barley and brown rice, with concentrations of 718, 389, 326, 302, 250, 199, 190 and 123 nmol/g DW, respectively (Oh et al., 2003a).

### 3.2. Dairy products

Cheeses, yogurt and fermented milk are the products that have been studied most for GABA enrichment by LAB, and many of them have potential in the management of hypertension. Cheese naturally enriched in GABA (16 mg of GABA/50 g of cheese), using *Lactococcus lactis* ssp. *lactis* strain as a starter, decreased blood pressure by 3.5 mmHg (Pouliot-Mathieu et al., 2013). Another cheddar cheese with a probiotic strain showed a higher GABA level than a control cheese (Wang, Dong, Chen, Cui, & Zhang, 2010).

GABA-enriched yogurt has also been obtained by different procedures (Park & Oh, 2006). Some commercial cheese starters were found to produce GABA, which increased during ripening in a skim milk culture (Nomura et al., 1998). Naturally fermented milk in Tibet had higher GABA levels than a commercial yogurt (Sun et al., 2009). Numerous studies on GABA enhancement in fermented milk have been reported, and many of them were found to have a hypotensive effect on rats (Hayakawa et al., 2004; Liu et al., 2011) and humans (Inoue et al., 2003; Nejati et al., 2013). Due to a mixed lactic acid bacteria starter, fermented goat's milk reached a GABA concentration of 28 mg/kg (Minervini, Bilancia, Siragusa, Gobbetti, & Caponio, 2009) and 500 mg/100 ml was obtained in fermented milk by the action of two lactic acid strains isolated from old-style cheese (Lacroix, St-Gelais, Champagne, & Vuillemard, 2013). A range of 15–99.9 mg/kg of GABA was obtained in a skim milk from several LAB-producing strains isolated from Italian cheeses (Siragusa et al., 2007) and *Lactobacillus helveticus* showed good potential (113.35 mg/L) in a fermented skim milk, and could potentially be used in the management of hypertension (Sun et al., 2009). A dose of 10–12 mg of GABA in 100 ml of fermented milk significantly decreased BP within 2 or 4 weeks in a randomized, placebo-controlled trial in mild hypertensive patients (Inoue et al., 2003). One strain of *L. plantarum* produced 77.4 mg/kg of GABA after milk fermentation and, in combination with other lactic acid bacteria, GABA reached a concentration of 144.5 mg/kg, which is considered a suitable dosage for a mild hypertensive effect (Nejati et al., 2013).

The evidence of a GABA-hypotensive effect on rats has even been widely reported in milk fermented products. Systolic and diastolic BP in spontaneously hypertensive rats (SHR) significantly decreased after a diet of GABA-enriched skim milk (970 ppm) fermented by *L. plantarum* (Liu et al., 2011). Arterial pressure was also lower in SHR after 8 weeks of oral administration of fresh, low-fat GABA-enriched milk (80.6 mg/100 g) fermented with five mixed lactic acid bacteria and with added protease. Another non-fat fermented milk has a hypotensive effect on SHR and in normotensive rat at a low dose (Hayakawa et al., 2004).

### 3.3. Meat, vegetables and legumes

Meat, fish, soybean and vegetables are a group of fermented products that are also used for GABA-enhancement, and several techniques have been proposed in this area. Meat enriched with GABA (Dai et al., 2012) and enriched feedstuffs (Matsunaga, Saze, Matsunaga, & Suzuta, 2009) may relieve animal stress so that quality, nutritional meat can be produced. Fermented pork sausage was enriched with GABA using specific LAB starter cultures (Ratanaburee, Kantachote, Charernjiratrakul, & Sukhoom, 2013) and fig proteases (Li et al., 2009a) to add value to the meat. A high content of GABA was detected in a traditional Japanese lactic-acid fermented fish (Kuda et al., 2009).

Vegetables enriched with GABA have been proposed for health: studies have been carried out on mustard leaf (Kim et al., 2013) and a patent has been issued for cruciferous plants (Hattori, Tsusaki, & Tagaki, 2005). The effects of GABA-containing vegetables on the cardiac autonomic nervous system have been studied in young people (Okita et al., 2009) and the results highlight the benefits of GABA on sympathetic nerve activity. In a fermented *Brassica* product, lactic acid fermentation produced a high GABA concentration, which suggests that this product could be used as a new functional food material (Norimura et al., 2009).

Legumes enriched with GABA, particularly beans, have also been studied. Recently, Liao, Wang, Shyu, Yu, and Ho (2013) proposed specific processes and fermentation conditions for GABA enrichment in *adzuki* beans, to provide a new, natural functional food resource. Black soybean was used to produce GABA-enhanced fermented milk as an antidepressant candidate (Ko, Victor Lin, & Tsai, 2013). A novel tempeh-like fermented soybean with a high level of GABA was developed with a specific cultivation procedure (Aoki et al., 2003). Other studies have simulated effects such as hypoxia and drought stress. These conditions were found to affect GAD activity and, hence, GABA accumulation, in soybeans nodules (Serraj, Shelp, & Sinclair, 1998). Moreover, Torino et al. (2013) showed high GABA concentration as a potent antihypertension compound in the fermentation of lentils.

### 3.4. Beverages

Research on different types of GABA-enriched beverages has recently been published. In particular, Chinese teas have been widely studied. A total of 114 samples from 6 types of tea were analysed and it was concluded that white tea had higher GABA content than other types (Zhao et al., 2011).

Levels of GABA can be enhanced in juices, mainly by lactic acid fermentation (Di Cagno et al., 2009; Hirose et al., 2008; Kim et al., 2009; Song, Shin, & Baik, 2014) or by specific fruit cultivation processes (Tamura et al., 2010). An experiment on the durability of GABA in fruit juices during storage at different temperatures and after radiation was reported and it was concluded that GABA remains stable (Shimizu & Sawai, 2008).

The antihypertensive effect and the relief of fatigue after the consumption of beverages containing GABA were demonstrated in rats (Hiwatashi, Narisawa, Hokari, & Toeda, 2010) and in Japanese subjects (Kanehira et al., 2011), respectively.

Finally, an alcoholic Japanese beverage was found to contain a high GABA level, due to the growth of a GABA-producing lactic acid strain in the medium (Yokoyama et al., 2002).

### 3.5. *Other enriched foods*

Other food products have been used to enhance GABA levels and provide health effects. An increased concentration of GABA in potato tubers and the antihypertensive effect of a GABA-enriched potato snack (Noguchi et al., 2007) and enrichment in chocolate (28 mg of GABA in 10 g of chocolate) to provide a psychological stress-reducing effect (Nakamura, Takishima, Kometani, & Yokogoshi, 2009) have been demonstrated in rats and in human subjects, respectively. Another study showed a GABA content ranging from 16 to 61 mg/100 g FW in 22 varieties of potato (Nakamura, Nara, Noguchi, Ohshiro, & Koga, 2006).

GABA concentration has also been analysed in a great number of uncooked food products. Foods with GABA concentrations above 100 nmol/g DW are: brown rice germ, brown rice sprouts, barley sprouts, bean sprouts, beans, corn, barley, brown rice, spinach, potatoes, sweet potatoes, yams, kale and chestnuts. The vegetables spinach, potatoes, sweet potatoes, yams and kale contain 414, 166, 137, 129, 122 nmol GABA/g DW, respectively. The GABA concentration of chestnut is 188 nmol/g DW (Oh et al., 2003b).

## 4. Future trends and conclusion

Hypertension is one of the major causes of cardiovascular disease, which, in turn, is the main cause of death in the world. It is therefore necessary to take precautions to prevent the epidemic. The pharmaceutical industry is associated with the food industry in a modern framework that promotes the inclusion of bioactive molecules in food to help control some diseases. In fact, the development of functional foods has been a key area of nutritional research in economically powerful countries, as a result of the experience gained in recent decades. However, there is a current perception that bioactive compounds are obtained primarily synthetically. Therefore, the exploration of bioactive molecules from natural sources is important in the discovery of new compounds. The main interest in the short- and medium-term is to research the effective dose of bioactive compounds if added both in isolation and as they occur naturally in the food matrix. The increasing development of functional foods is marked by the tendency of consumers to promote and maintain their health. Indeed, the functional food market will grow by combining credible science with an understanding of consumers and their beliefs. Furthermore, the increased market share of novel food is of great benefit to the food industry. GABA research has been intensified in recent years, with numerous scientific studies clinically demonstrating its benefits in many physiological disorders, and particularly in hypertension, as GABA contributes efficiently to the regulation and stability of blood pressure. The generation of GABA from glutamic acid or its salt in probiotic cells and other natural resources such as plants or fungi is of added value to the food industry, because of the notable increase in interest in natural and organic foods. Industrial scale production of GABA from marine sources may not be able to compete economically with lactic acid bacteria production. High performance production, optimization through different biotechnological techniques, and the discovery of new high-GABA producing strains will remain a focus of interest in research into GABA as a health-related novel biological active compound. Testing and validation is yet another important step in increasing the prospects for clinical trials of bioactive molecules.

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